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Parity and Heart Failure in Postmenopausal Women

Erin Dingman

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Methods: An exhaustive search of available medical literature was performed. MEDLINE OVID, CINAHL, and Web of Science databases were searched using the keywords nulliparity, postmenopause, and heart failure. The articles were evaluated using GRADE.

Results: The search resulted in 2 studies evaluating the incidence of heart failure in a postmenopausal population and accounting for gravidity.

Conclusion: There is an association between nulliparity, grand multiparity, and increase in risk of heart failure in the postmenopausal population. The strongest association can be seen in development of heart failure with preserved ejection fraction.

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Parity and Heart Failure in Postmenopausal Women

Erin A. Dingman

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Faculty Advisor: Craig T. Turner, MD

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS

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List of Abbreviations

HF…….....…Heart Failure
HFrEF……...…. Heart Failure with reduced Ejection Fraction
HFpEF……...…. Heart Failure with preserved Ejection Fraction
ICD.....International Classification of Disease
HR……..…Hazard Ratio
WHI…….Women's Health Initiative

Parity and Heart Failure in Postmenopausal Women

BACKGROUND

Nulliparity is defined as never having been pregnant or never completing a pregnancy beyond 20 weeks gestation. High (or grand) parity is classified as greater than or equal to 5 births. Heart failure (HF) may be classified as either diastolic HF (also termed heart failure with preserved ejection fraction (HFpEF)) or systolic HF (also termed heart failure with reduced ejection fraction (HFrEF)).

With the increase in incidence of HF in the US population, determining risk factors in female patient populations can enable better management of care. The Framingham Heart Study[1] reported a lifetime risk of heart failure development in women at 1 in 6, with poorly managed hypertension identified as the major risk factor in development of future disease. Furthermore, the incidence of heart failure diagnosis increased with advancing age.[1] Coronary heart disease, tobacco abuse, hypertension, obesity, diabetes mellitus, valvular disease and ethnicity are the typical qualities noted in a patient history that may influence one's risk for heart failure diagnosis.[2]

Heart failure is also known to occur in women in the peripartum setting, most commonly brought on by peripartum cardiomyopathy or hemodynamic changes, leading to exacerbation of symptoms in those with a previous diagnosis of heart failure.[3] This raises the question, how does parity influence the risk for development of HF in a postmenopausal population?

METHODS

An exhaustive search of available medical literature was performed. MEDLINE-OVID was searched, utilizing the terms "parity or nulliparity", "heart failure or cardiovascular diseases", "adult" and "aged". CINAHL and Web of Science databases were searched using the terms "parity or nulliparity", "heart failure or cardiovascular diseases", and "aged". Eligible articles included cohort studies published within the last 10 years with postmenopausal women as the population of interest. Studies referenced incidence of heart failure, postmenopause, in relation to the number of pregnancies of participants to infer risk assessment. The articles were assed for quality using Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).[4] See Figure I.

RESULTS

The MEDLINE-OVID search yielded 139 results when limited to articles published in the English language. Two articles[5,6] were identified evaluating the incidence of heart failure in a postmenopausal population and accounting for gravidity. CINAHL yielded 13 results with one identified article which was a duplicate. The Web of Science search yielded 56 results with 2 articles of interest, again duplicates. See Table I.

In 2009, publication[6] of research directly addressing a relationship between parity and incident HF in a population of Swedish postmenopausal women was published. Results from this analysis demonstrated risk association with development heart failure in older women (≥50 years) in a J-shaped pattern. In a study population of 1 332 062 women, 6069 heart failure events were identified during the study period by *International*

Classification of Diseases, Ninth Revision (ICD-9) or *International Classification of Diseases, Tenth Revision* (ICD-10) diagnosis obtained from a first hospitalization or death of an identified participant as recorded in the Hospital Discharge Register and Cause of Death Register. Women with 2 births were used as the reference. Women who were nulliparitus, had one birth, or more than 4 births were more likely to have a reported ICD-9 or ICD-10 diagnosis for heart failure than women with 2 or 3 births. Hazard ratios (HR) for incident heart failure based on parity (0, 1, 2, 3, 4, and ≥5 births), in an age adjusted model were reported as 1.71, 1.36, 1.0, 1.13, 1.39, and 2.21 ($p<0.0001$) respectively. Hazard ratios (HR) for incident heart failure based on parity (0,1,2,3,4, and ≥5 births), in an age, birth year, and socioeconomic adjusted model were reported as 1.78, 1.35, 1.0, 1.10, 1.31, and 1.91 ($p<0.0001$) respectively.[6] See Table II.

In 2017, a second study[5] focused on HF and parity was published. Using data from the Women's Health Initiative (WHI), investigators examined data to identify a relationship between parity, reproductive duration, and age at first pregnancy with HF in a postmenopausal population. The WHI population of 28 516 postmenopausal women identified 1494 incidents of heart failure either by confirmed HF hospitalization or patients self-reporting, and subsequent adjudication by a physician review of records. Results demonstrated nulliparity was associated with a statistically significant increased risk of HFpEF in both age-adjusted (HR: 2.57; 95% CI:1.22 to 5.44) and multi-variable adjusted models (HR 2.75; 95% CI: 1.16 to 6.52)[5]. See Table III. When assessing for 0, 1, 2, 3, 4, and ≥5 births the respective age adjusted HRs were 1.80, reference, 1.05, 1.03, 1.12, and 1.13 and multivariable –adjusted HRs of 1.70, reference, 1.13, 1.17, 1.19, and 1.15[5]. See Table II.

DISCUSSION

Analysis of both cohorts have shown low and high parity are associated with more pronounced risks for heart failure[5,6] with the least risk identified at 1-2 births. Stronger evidence of this phenomena is demonstrated in the Swedish cohort than in the WHI cohort, see Table II. High parity holds the greatest risk of heart failure events[5,6]. Interestingly, when data was analyzed to identify risk in women whose children were all parented by the same partner, the extent of risk was slightly reduced as compared to women with children by multiple partners. Both populations retained the J-shaped risk distribution.[6]

The studies [5,6] included in this review have demonstrated a moderately strong increase in risk of HFpEF diagnosis, hospitalization, or cause of death in women without history of pregnancy. Evaluation of the Swedish cohort[6] was able to demonstrate a statistically significant relationship between total incident HF/total number of events ($P < 0.0001$; HR 1.71, CI: 1.59-1.84), whereas the WHI cohort did not have a statistically significant correlation (HR 1.70, CI: 0.95-3.03).

Despite the results, both studies[5,6] had limitations. In the WHI cohort,[5] results comparing nulliparitus women and Total Incident HF, Incident HFrEF and Incident HFpEF all demonstrated small sample sizes for nulliparitus women, ranging from 182-188 women out of study populations in excess of 28 000. The small sample size may limit the significance of the statistical findings of this study population. While the WHI population represented a more ethnically diverse sample population, the Swedish cohort did not provide a racial breakdown of participants, and recognized the rather homogenous

nature of the Swedish population. Future research with a focus population of women of varying ethnic backgrounds may yield data with greater validity for a risk relationship. Neither study identified contraceptive methods used by nulliparitus women. Future research could include hormonal contraceptive usage data to identify if treatment with estrogen, progesterone, or a combination therapy influences future diagnosis of HF.

CONCLUSION

Both nulliparity and high parity have been shown to increase the risk of development of heart failure in a postmenopausal population. Hazard ratio estimates ranging from 1.70 – 1.78 demonstrate nullliparitus women have slightly less than a two-fold increase in risk of developing heart failure at older ages than women with 1-4 live births. Women whom have had given birth 5 or more times have a 2-fold increase in risk of heart failure events, as compared to women with 1 or 2 births. Hormonal or hemodynamic changes which take place during pregnancies may lead to cardioprotective characteristics in women who have bore children, but this protective effect seems to be offset in the setting of high parity. This research may assist health care providers in recognizing other qualities in a patient's social history that play a role in risk management.

References

1. LloydJones DM, Larson MG, Leip EP, et al. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation*. 2002;106:3068-3072.
2. Vasan RS., Wilson PWF. Epidemiology and causes of heart failure. In: Colucci WS, Yeon, SB, ed. *UpToDate*. Waltham, Mass.: UpToDate, 2018. https://www.uptodate.com/contents/epidemiology-and-causes-of-heart-failure. Accessed January 26, 2018.
3. DeCara JM, Lang RM, Foley MR. Management of heart failure during pregnancy. In: Colucci WS, Lockwood CJ, Yeon SB, ed. *UpToDate*. Waltham, Mass.: UpToDate 2018. https://www.uptodate.com/contents/management-of-heart-failure-during-pregnancy. Accessed January 3, 2018.
4. GRADE working group. GRADE website. http://gradeworkinggroup.org/. Accessed June 10, 2018.
5. Hall PS, Nah G, Howard BV, et al. Reproductive factors and incidence of heart failure hospitalization in the women's health initiative. *Journal of the American College of Cardiology*. 2017;69(20):2517-2526. doi:10.1016/j.jacc.2017.03.557.
6. Parikh NI, Cnattingius S, Dickman PW, Mittleman MA, Ludvigsson JF, Ingelsson E. Parity and risk of later-life maternal cardiovascular disease. *American Heart Journal*. 2010;159(2):215-221.e6. doi:10.1016/j.ahj.2009.11.017.

Table I: Quality Assessment of Reviewed Articles

Study	Design	Downgrade Criteria					Upgrade Criteria	Quality
		Limitations	Indirectness	Inconsistency	Imprecision	Publication bias		
Hall, et al	Observational	Not Serious	Not Serious	Not Serious	Not Serious	Unlikely		Low
Parikh, et al[2]	Observational	Not Serious	Not Serious	Not Serious	Not Serious	Unlikely		Low

Table II. Heart Failure Incidence in Female populations based on parity

Study	Parity	Recorded HF Events	Recorded HF Events per 1000 Person-Years	Age Adjusted Model HR (95% CI)	P value Across Group	Multivariable Adjusted Model HR (95% CI)	P value Across Group
Parikh et al							
	0	1064	0.59	1.71 (1.59-1.84)	<0.0001	1.78 (1.65-1.93)	< 0.0001
	1	1094	0.48	1.36 (1.26-1.46)		1.35 (1.25-1.45)	
	2	1950	0.34	1		1	
	3	1166	0.40	1.13 (1.05-1.21)		1.10 (1.03-1.19)	
	4	464	0.53	1.39 (1.26-1.54)		1.31 (1.18-1.45)	
	≥ 5	331	0.88	2.21 (1.97-2.49)		1.91 (1.70-2.15)	
Hall et al							
	0	16	0.75	1.80 (1.07-3.03)	0.21	1.70 (0.95-3.03)	0.48
	1	138	0.34	Reference (N/A)		Reference (N/A)	
	2	332	0.36	1.05 (0.86-1.28)		1.13 (0.91-1.41)	
	3	358	0.39	1.03 (0.84-1.25)		1.17 (0.94-1.45)	
	4	287	0.44	1.12 (0.91-1.38)		1.19 (0.95-1.50)	
	≥ 5	363	0.50	1.13 (0.92-1.38)		1.15 (0.92-1.45)	

Abbreviations: HF, heart failure; HR, hazard ratio
Swedish cohort N = 1 332 062; WHI cohort N = 28 515

Table III. Nulliparity and Differentiated Heart Failure Incidence

Study	HF Classification	Reproductive Factor	Number of Women	Hazard Ratio (95% CI)
Hall et al				
	Total Incident HF	Nulliparitus	188	1.70 (0.95-3.03)
	HFrEF	Nulliparitus	182	1.27 (0.39-4.17)
	HFpEF	Nulliparitus	186	2.75 (1.16-6.52)

Abbreviations: HF, heart failure; HFrEF, heart failure with reduced ejection fraction (systolic HF), HFpEF, heart failure with preserved ejection fraction (diastolic HF); CI, confidence interval
WHI cohort N = 28 515
HR adjusted for age at screening, household income, education level, ethnicity, U.S. region, body mass index, hypertension, diabetes, hyperlipidemia, smoking status, breastfeeding, history of pregnancy loss, prior hysterectomy, and usage of oral contraception or menopausal hormone therapy

Figure I. PRISMA Flow Diagram